ADA American Dental Association®

1111 14th Street, N.W.
Suite 1200
Washington, DC 20005

T 202.898.2400
F 202.898.2437
www.ada.org

December 15, 2018

Griffin Rodgers, M.D., M.A.C.P.
Chair
NIH Nutrition Research Task Force
c/o National Institute of Diabetes and
Digestive and Kidney Diseases
Building 31, Room 9A06
31 Center Drive, MSC 2560
Bethesda, MD 20892-2560

Christopher J. Lynch, Ph.D.
Executive Secretary
NIH Nutrition Research Task Force
c/o National Institute of Diabetes and
Digestive and Kidney Diseases
Building 31, Room 9A06
31 Center Drive, MSC 2560
Bethesda, MD 20892-2560

Dear Drs. Rodgers and Lynch:

On behalf of our 161,000 dentist members, we are pleased to comment on the NIH Nutrition Research Task Force's (NRTF) draft Strategic Plan for NIH Nutrition Research. We offer these comments in response your request for information of November 21, 2018 (NOT-DK-19-004).

The NRTF's Strategic Plan will help guide the next decade of NIH-supported nutrition research. It is comprised of seven dovetailing themes that identify critical knowledge gaps in human nutrition research. Further, it establishes cross-cutting opportunities to close those knowledge gaps through basic science, experimental design and training.

We applaud the NRTF for recognizing how the field of human nutrition research can be strengthened by conducting more cross-cutting research. Science has been pointing to an interdependent relationship between diet, nutrition and oral health for some time. Unfortunately, the draft plan contains no mention of dental caries, few mentions of the oral microbiome and few opportunities to address critical knowledge gaps in the area of oral health and poor nutrition.

As you can see from the enclosed comments, there are several areas we would like the plan to address. Our comments may be summarized as follows:

- We are concerned that the number one chronic childhood disease—dental caries—is not listed as one of the *top* diseases associated with poor nutrition.

- We are concerned by the few mentions of the oral microbiome and its relationship to the gut microbiome.

- We agree that better research methods are needed to determine what conditions and combination of strategies have the greatest potential to foster healthy eating in real-world settings and whether and how those patterns can be sustained over time.

The field of nutrition science can benefit from more research dissecting the relationship between diet, nutrition and oral health. The Strategic Plan for NIH Nutrition Research is an opportunity to promote more interdisciplinary research in that area.

Again, we urge you to incorporate the enclosed changes in the draft strategic plan. Doing so would be a sign of progress in advancing the oral health goals and objectives in Healthy People 2020. It would also reinforce the dramatic shift in the way people view oral health—as an essential part of overall health and well-being.

If you have any questions, please contact Mr. Robert J. Burns at 202-789-5176 or burnsr@ada.org. Information is also available at ADA.org/nutrition.

Sincerely,

/s/

Jeffrey M. Cole, D.D.S., M.B.A., F.A.G.D
President

/s/

Kathleen T. O'Loughlin, D.M.D., M.P.H.
Executive Director

JMC:KTO:rjb

ADA American Dental Association®

Draft Strategic Plan for NIH Nutrition Research
Detailed Comments and Recommendations

December 15, 2018

The American Dental Association is pleased to offer the following comments and recommendations on the NIH Nutrition Research Task Force's (NRTF) draft Strategic Plan for NIH Nutrition Research.

- ***We are concerned that the number one chronic childhood disease—dental caries—has not been identified as one of the top diseases associated with poor nutrition.***

  Dental caries is the most common chronic disease of children aged 6 to 11 years and adolescents aged 12 to 19 years. Tooth decay is four times more common than asthma among adolescents aged 14 to 17 years. Dental caries also affects adults, with 9 out of 10 over the age of 20 having some degree of tooth-root decay.[1]

  Science has been pointing to an interdependent relationship between diet, nutrition and oral health for some time. Unfortunately, there is still a need for scientific research in the field. For example, there a moderate degree of consistent evidence indicating dental caries would be lower when free-sugar(s) consumption is less than 10 percent of energy intake, and a low degree of consistent evidence when the energy intake cutoff is 5 percent.[2]

  Research is also needed to determine whether low-pH level acids increase the risk for dental caries, either alone or in conjunction with sugar.

  We understand the methodological challenges of investigating the relationship between added sugar(s) and dental caries, which is a multifactorial disease. One of the strategic plan goals is to develop more reliable methodologies. We hope that will include novel methodologies to further research in this area.

- ***We are concerned by the few mentions of the oral microbiome and its interdependent relationship to the gut microbiome.***

  The overwhelming theme in our comments is that the draft plan contains few mentions of the oral microbiome and its relation to overall health as well as its relationship to the gut microbiome. We urge you to clarify throughout the document, and perhaps in the glossary, whether 'gut' is being used as a comprehensive term to encompass the community of microrganisms colonizing the intestines and the oral cavity or refers solely to those communities found in the stomach and intestinal tract.

  Given that the composition of the oral microbiome is distinct from the GI microbiome but has been documented to be influenced the foods that are consumed, the oral microbiome should be specified and referenced as another microbiome to be studied.

  One pioneering area of dental research examines the utility of saliva for use to monitor micro and macro nutrient intake. If successful, salivary diagnostic tests might be

developed to readily assess an individual's dietary patterns and be used to guide recommendation to reduce their risk for type-2 diabetes.

- ***We agree that better research methods are needed to determine what conditions and combination of strategies have the greatest potential to foster healthy eating in real-world settings and whether and how those patterns can be sustained over time.***

  Questions remain about whether reducing total added sugar intake from present levels will reduce dental caries rates over time. Research is also needed to determine means to mitigate the effect consumption of low-pH beverages and food on dental erosion.

  We understand the methodological challenges of investigating the relationship between added sugar(s) and dental caries, which is a multifactorial disease. The amount of sugar an individual consumes is certainly a factor, but so is the frequency and duration of exposure, along with salivary flow, water consumption patterns and oral hygiene.

  One of the strategic plan goals is to develop more reliable methodologies. We hope that will include novel methodologies to further research in this area.

In accordance with these general comments, the ADA recommends the following edits to the draft Strategic Plan for NIH Nutrition Research.

BACKGROUND AND SIGNIFICANCE

Beginning p. 6, first full paragraph:

"Nutrition encompasses the processes involved in ingesting food and dietary components and their absorption and utilization for growth and development, metabolism, repair, and health maintenance. Nutrition is integral to the prevention and treatment of disease as well as for health promotion. Poor nutrition contributes to some of the leading causes of death and increases the risk of numerous diseases, including heart disease, diabetes, obesity, dental caries, high blood pressure, stroke, cancer, and osteoporosis. Improving nutrition has the potential to be one of the most cost-effective health care strategies for reducing human morbidity and mortality across the world."

THEME 1: INVESTIGATE NUTRITIONAL BIOCHEMISTRY, PHYSIOLOGY, AND THE MICROBIOME

Beginning p. 17, first full paragraph:

Scientific Priorities

1-2. Clarify the Integrative Physiology of Ingestive Behaviors

"This Priority focuses on how nutrient information is transmitted throughout the body, and the integration of information to regulate metabolism, physiology, and behavior. Integrative

physiological pathways responsible for ingestive behaviors, including their associated biological, psychological, and social processes, need to be clarified. Examples of these pathways include oral and gut-brain signaling by incretins, bile acids, vagal-vagal or gastrointestinal (GI) hormones, central nervous system (CNS) monitoring of nutrient status, and the mechanisms involved in translating the signaling into behavioral, metabolic, or physiological responses. Work is also needed to understand how external, internal, and circadian cues, and their interactions, affect these pathways.

Research is needed to clarify the functional effects of and integrative pathways responsible for nutrition-related ~~GI~~ peptides, hormones, and vagal activation, as well as adipose-derived lipokines, adipokines, cytokines, and small nucleic acids. This research could take advantage of new neuromodulatory technologies, including vagal nerve stimulation and blocking, in combination with imaging and blood sampling to elucidate mechanisms and pathways involved in normal and disrupted eating behaviors."

Beginning p. 18, first full paragraph:

1-3. Identify and Leverage Interrelationships between Diet, Host, and Oral and Gut Microbiomes Promote Health

"~~Individual gut~~Oral and gut microbiota (including bacteria, fungi, Archea, bacteriophages, and viruses) have sometimes been designated as either beneficial or pathogenic. However, the oral and gut microbiota increasingly ~~has~~have been recognized as ~~an~~ ecosystems based on symbiotic relationships (mutualism, commensalism, and parasitism) between members of the microbial communities and between these communities and the host. Recent research has revealed evidence of metabolic niches and microbial community metabolism in which individual species are responsible for different metabolic steps. Research is needed to clarify these niches, their community metabolism, and how diet may affect them.

Investments to improve methods and resources have led to a tremendous leap forward in the ability to pursue research on the oral and gut microbiomes~~(the collective genomes of the microbes that live inside and on the human body)~~. This increased accessibility has fueled a groundswell of preclinical and clinical studies exploring potential roles of the oral and gut microbiomes in integrative physiology, health, behavior, and a broad range of chronic diseases.

Despite the recognition of the potential for food to affect microbiota metabolism in the gut, and to a lesser extent the species diversity, only a fraction of microbiome research has collected data on the diet or nutritional status of the host. Researchers have a tremendous opportunity to better understand how dietary components or dietary patterns affect the host through the oral and gut microbiomes, to elucidate the underlying mechanisms and pathways—including the oral and gut microbiomes-brain axis—and to leverage these interrelationships to promote the health of the host. Facilitating improvements in research practices related to the inclusion of diet and nutrition considerations in microbiome research is a priority."

Beginning p. 19, second full paragraph:

1-3a. Identify Best Practices in the Design of Research Examining Interrelationships Between the Host, Oral and Gut Microbiomes*, and Diet*

"Another opportunity to improve rigor and reproducibility pertains to both preclinical and clinical microbiome research, where careful consideration should be given to the selection of diet. The rationale for the choice of diet should be factored into the analysis and carefully reported in scientific communications. Attention should be focused on the type of dietary fiber (soluble versus insoluble) and whether it is metabolizable (accessible) by the microbiota or not. The chemical diversity of dietary fibers may present opportunities for selectively engaging microbiota-mediated metabolic pathways and should be taken into consideration when designing an experimental diet. The micronutrient and polyphenol content of the diet should also be considered, as these will affect microbial ecology, including microbiota composition and metabolic activities. Additionally, dietary manipulations to reflect the various types of diets consumed by different populations could provide information on oral and gut microbial flora associated with these dietary patterns. The timing between diet interventions and microbiome sampling should also be considered and should be based on known transit times in the oral and GI regions of interest.

The following information is frequently obtained as part of clinical diagnostic investigations for digestive disorders: 1) the total number of microbes in a fecal sample, 2) stool quality (e.g., as measured by the Bristol Stool Scale), and 3) bowel habits. However, this information is not consistently collected in microbiome research studies. Collecting these standard measures of digestive health is a third area that could benefit gut microbiome research. Culture-independent methods, such as those based on analysis of 16S ribosomal RNA gene community profiling, can also be used to characterize the oral microbiome.

Future research activities that could be pursued in this Priority include, but are not limited to, the following:

- Prospectively investigate ~~the role of~~associations between the microbiome ~~in the development of~~and diet-related health outcomes.

- Elucidate the optimal range of times between the start of a dietary intervention and assessments to examine the consequences of that intervention on oral and gut microbial ecology.

- Elucidate the bidirectional interactions between the host's diet, genome, metabolome, and ~~gut~~ microbiomes and determine the diet-related factors that ~~lead to the development of stable microbiome~~minimize microbiome dysbiosis during childhood."

Beginning p. 20, third full paragraph:

1-3b. Encourage Development of Bioinformatic Resources and Tools

"Several approaches could be explored to foster research in this area. Improving the annotation of metabolomic and proteomic libraries is one of them. The knowledge of metabolites produced by the oral and gut microbiota is very limited, and it is not known which of those molecules are derived from dietary sources. Improving this knowledge and developing a database of spectral features from fresh and prepared common foods (and food-based metabolites) along with partially digested oral or gut microbiota metabolized food is urgently needed. These data should be incorporated into existing databases.

A second important opportunity involves studies to elucidate microbial-mediated metabolic pathways. Further research is needed to understand the ecological flow of dietary substrates and their microbial metabolism in the oral cavity and gut, especially for microbial metabolites that affect the host. Diet serves as a substrate to produce metabolites that may have a significant effect on host physiology in health and disease and can affect the species composition of the oral and gut microbiomes. Dental caries, gingivitis, and periodontitis are the most common disease states and they result from dysbiosis of the oral ecosystem.

Permitting real-time monitoring of oral and GI metabolites along with in situ sampling of, and delivery of metabolites to, discrete regions of the oral cavity and GI tract is a third potentially fruitful avenue for research in this area. Nutrient and metabolite signaling in discrete regions of the oral cavity and GI tract may be important for tastant, incretin, oral and GI reflexes (e.g., through gut-brain axis or enteroendocrine responses), and inflammation of the oral mucosa and gastrointestinal-associated lymphoid tissues. Many discrete gut regions, such as the jejunum, ileum, and cecum, are presently inaccessible by endoscopic or other approaches in conscious, fed individuals. New tools and technologies that would allow study of the microbiome in situ and in discrete regions of the gut could advance the field and better clarify the regional differences and dynamic nature of the responses of the microbes to diet. Moreover, such sampling could facilitate studies comparing mucosal versus luminally associated microbes.

Future research activities that could be pursued in this Priority include, but are not limited to, the following:

- Determine the molecular identity of unknown mass spectrometric signatures associated with microbial metabolism of ingested foods.
- Elucidate metabolic pathways that require enzymatic activities of multiple microorganisms, especially for metabolites of physiological or pathological significance for the host.
- Identify changes to the oral microbiome in response to diet.
- Identify microbiota and metabolites in chyme from distinct regions of the gut after meal challenge or diet interventions.
- Investigate host-gut microbiota co-metabolites such as bile acids."

Beginning p. 21, next to last paragraph:

1-3c. Discover Mediators, Mechanisms, and Translational Roles of Diet-Host-~~Gut~~ Microbiota Interrelationships

"Oral and gut microbes not only influence what the human host is able to extract from the diet, both nutritionally and energetically, but also may affect host physiology, behavior, and susceptibility to diet-related chronic disease. Research into the associations between diet and the oral and gut microbiomes is needed to further elucidate their bidirectional interactions, and how prebiotics, probiotics, and synbiotics influence these associations.

One goal of this Theme is to expand knowledge about how diet-~~gut~~ microbiome interactions affect host physiology and behavior. Identifying the mechanisms underlying microbiome-mediated effects on health and disease susceptibility could lead to new therapeutic targets. Another goal is to identify roles of the regional ~~GI~~ microbial ecologies in host biology and health as well as their physical importance. Microorganisms in other gut regions, which may be closer to major axes of nutrient signaling and regulation would be of interest, as they may be more dynamic or responsive to diet than those of the cecum.

Future research activities that could be pursued in this Priority include, but are not limited to, the following:

- Develop methods to produce stable isotope-labeled dietary fibers and oligosaccharides that are digestible by the oral and gut microbiota but not directly by the host.
- Determine the mechanisms by which diet influences the oral or gut microbial ecosystems to bring about changes in host biology, behavior, and health.
- Determine whether bioactive microbial metabolites, have a physiologic impact on human mucosal immunity and cardiovascular disease risk.
- Elucidate the roles of regional gut microbiota from oral cavity to colon and identify diet-dependent variability in these regional ecosystems and the consequences for the host.
- Investigate variations in microbial composition as a function of age and in the elderly."

THEME 2: ASSESS THE ROLE OF NUTRITION AND DIETARY PATTERNS IN DEVELOPMENT, HEALTH, AND DISEASE ACROSS LIFE STAGES

Beginning p. 30, second full paragraph:

Scientific Priorities

2-5. Determine Mechanisms by which Dietary Patterns Affect Health Status and Chronic Disease Susceptibility

2-5a. Provide Mechanistic Insights into Dietary Patterns and Chronicity to Reduce Chronic Diseases

"Research designed to study the impact of dietary behaviors that involve the frequency of food consumed or the timing of when food is eaten may also provide valuable insights. Energy metabolism is not static and may require precise coordination of behavior, physiology, and molecular process across the 24-hour cycle. Mounting evidence links circadian misalignment to an array of adverse health conditions, including obesity, diabetes, xerostomia, hypertension, stroke, cancer, and GI disorders. Thus, research suggests that behaviors such as the number of meals or eating occasions per day, meal skipping, and hours between eating occasions and/or fasting all have biological consequences. Further investigation is needed to elucidate the pathways behind these effects."

THEME 3: EXPLORE INDIVIDUAL VARIABILITY IN RESPONSE TO DIET INTERVENTIONS TO INFORM NUTRITION SCIENCE, IMPROVE HEALTH, AND PREVENT DISEASE

Beginning p. 33, second full paragraph:

Introduction

"Such inter-individual variability in responses extends to nutrition interventions, even in genetically identical preclinical models. A wide range of factors is thought to have a role in an individual's physiologic response to diet and food components. These include, but are not limited to, genetics, epigenetics, metabolism, oral and gut microbiota diversity and metabolism, inflammatory status, sleep and exercise habits, environment (e.g., food access and exposure to toxins and/or pathogens), social and health disparities, socioeconomic factors, medication use, and the presence of disease or conditions. A tremendous opportunity exists to improve knowledge about how distinct dietary patterns and intake interact with these factors, and to study the comparative role and interaction of these factors on individual health outcome responses to dietary interventions. A key priority in this area is to test the efficacy and effectiveness of personalized intervention approaches tailored to individuals' genetic variants, microbiome, metabolic profiles, and above-mentioned or unknown factors compared with traditional "one size fits all" approaches in improving dietary quality and health outcomes. Overall, researchers need a better understanding of when population versus targeted/precision nutrition interventions will be optimal."

Beginning p. 34, third full paragraph:

Scientific Priorities

3-1. Elucidate the Biological Factors Underlying Individual Variation in Response to Dietary Interventions

"Relevant biological factors include, but are not limited to, genetics, epigenetics, oral and gut microbiota metagenomics, metabolomics, transcriptomics, anthropometrics, behavioral phenotype, chronotype, heart rate, GI transit times, and the presence of inflammation. These factors can be assessed with various tools, including health histories, clinical laboratory measures, electroencephalography, bioimaging, and sensor data. Whereas some behaviors affected by biology occur at the level of consciousness, others, such as hedonic responses to taste, salivation, oral microbiome acid production, rates of gastric emptying, incretin release and responses, and digestive responses occur subconsciously. Understanding the role of these factors in inter-individual responses to diet and nutrition is important. Of equal importance is the need to improve the current standards and tools used to assess nutritional status to determine normal intra-individual and inter-individual response to and metabolic utilization of some nutrients and dietary components. Establishment of such metrics would allow comparisons across diverse populations."

THEME 7: SUPPORT TRAINING TO BUILD AN OUTSTANDING NUTRITION RESEARCH WORKFORCE

Beginning p. 57, paragraph 3:

Introduction

"Among the important opportunities to improve research training in nutrition research, two areas in particular include: interdisciplinary training in research related to the oral and gut microbiomes and training in utilizing Big Data."

Beginning p. 57, paragraph 4:

Training Priorities

7-1. Facilitate Training in Host, Oral and Gut Microbiomes Metabolism, and Diet Interrelationships

"Investments in specialized training for research on host, oral and gut microbiomes, and diet interrelationships may be needed to support emerging research in this field, as described in Priority 1-3. Training in nutritional biochemistry may be essential to enhance knowledge about the complex interactions among nutrition, biochemistry, physiology, and metabolism by the host and microbiota."

Beginning p. 58, first full paragraph:

"Researchers seeking to understand diet and microbiome interrelationships will require training in the biochemistry of foods, including dietary glycomics (i.e., the chemical structure and source of dietary fibers) to learn how the biochemical diversity and sources of dietary fiber shift microbial metabolism and ecology. Training gaps for research on the microbiome include integrative and oral and GI physiology, ingestive behavior (including gut-brain communication), and the interaction between inflammation, nutritional requirements, and metabolism."

GLOSSARY

The draft plan contains few mentions of the oral microbiome and its interdependent relationship to the gut microbiome. We urge you to clarify throughout the document, and perhaps in the glossary, whether the oral microbiome is being considered separately from or part of the gut microbiome. In some instances, it is unclear.

Page 63, third term:

"**Microbiota**: The collective term for the microorganisms that typically inhabit an environment. The human microbiota consists of the symbiotic microbial cells harbored by each person, primarily bacteria in the gut and oral cavity."

Page 64, third term:

"**Prebiotics:** Food ingredients intended to promote the growth of beneficial oral cavity and gut microbes."

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[1] Dye BA, Tan S, Smith V, Lewis BG, Barker LK, Thornton-Evans G, Eke PI, Beltrán-Aguilar ED, Horowitz AM, Li CH. Trends in oral health status, United States, 1988-1994 and 1999-2004. Vital Health Stat 11. 2007;(248):1-92.

[2] Guideline: Sugars intake for adults and children. Geneva: World Health Organization; 2015.